DETAILED ACTION

1. Applicant's amendment and response filed 7/22/1 are acknowledged and have been entered.

2. Applicant is reminded of Applicant's election without traverse of Group II in Applicant's response filed 1/18/11, and species of SEQ ID NO: 1 and BMP-7 in telephonic interviews with Mr. Stephen Todd on 2/8/11 and 2/11/11.

Applicant is reminded that upon consideration of the prior art, the SEQ ID NO: 2-5 had been included in examination.

Claims 7-10 and 12-15 are currently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the priority claim for benefit of PCT/US04/34679 is under both 35 USC 119 and 35 USC 120. It should be under 35 USC 120.

4. Applicant is reminded that the use of the trademarks PEPSETS, MIMOTOPES, CELL-DYN, MICROBETA and LYMPHOPREP have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. Applicant's amendment filed 7/22/11 has overcome the prior rejection of record of claim 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

6. Claims 7-9 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant has claimed a method of reducing the immunogenicity of a bone morphogenetic protein (BMP), comprising the recited steps wherein at least one T cell

epitope of a BMP protein is identified by its ability to stimulate T cell proliferation and wherein the BMP protein is modified to produce a variant protein which induces less than or substantially equal to baseline proliferation of T cells by neutralizing said T cell epitope, wherein the amino acid sequence of said T cell epitope that is identified and neutralized is one of SEQ ID NO: 1-5.

The specification does not disclose a representative number of BMP proteins that comprise at least one of SEQ ID NO: 1-5 that are not BMP-7.

The specification discloses that SEQ ID NO: 1-5 were identified as originating from BMP-7 protein and are 15-mer peptides from an overlapping PEPSET of BMP-7 that can induce T cell proliferation (see Table 1 and Examples).

"Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

The specification discloses that there are at least fifteen BMP proteins (see page 1 at lines 21-36 and page 2 at lines 1-29), each having a different length and amino acid sequence, and some that have been identified in different species of mammals. The specification further discloses that "Bone morphogenetic protein" ("BMP") is the generic term used to refer to a family of proteins originally identified in demineralized bone extracts...While the term "BMP" is indicative of their properties, these proteins also have other functions and are involved in processes other than bone formation" (see page 1 at lines 15-19).

The specification defines BMP protein in functional terms, with no recitation of structure.

Therefore, it appears that the instant specification does not adequately disclose the breadth of bone morphogenetic protein in the claimed method of reducing immunogenicity. In light of this, a skilled artisan would reasonably conclude that Applicant was not in possession of the genus of all BMP proteins of the claimed method at the time the instant application was filed.

7. Claims 7-9 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the instant invention, a method of reducing the immunogenicity of a bone morphogenetic protein (BMP), comprising the recited steps wherein at least one T cell epitope of a BMP protein is identified by T cell proliferation and wherein the BMP protein is modified to produce a variant protein which induces less than or substantially equal to baseline proliferation of said T cells by neutralizing said T cell epitope, wherein the amino acid sequence of said T cell epitope that is identified and neutralized is one of SEQ ID NO: 1-5.

The specification has not enabled the breadth of the claimed invention because the claims encompass:

(1) a method for reducing the immunogenicity of any BMP of any amino acid sequence (instant base claim 7) or a method for producing a variant BMP protein having reduced allergenicity (instant base claim 14), wherein the T cell epitope that is identified and neutralized or modified, respectively, is one of SEQ ID NO: 1-5, and

(2) a method for reducing the immunogenicity of a BMP (including BMP-7) (instant base claim 7) or a method for producing a variant protein having reduced allergenicity (instant base claim 12) wherein the method comprises modifying the BMP protein to neutralize a subsequence of said BMP protein that is one of SEQ ID NO: 1-5, but also identifying SEQ ID NO: 1-5 as being capable of effecting T cell proliferation even though the claim already recites that one of SEQ ID NO: 1-5 is what is to be modified/neutralized (*i.e.,* the claim preamble recites a method of reducing immunogenicity or producing a variant BMP protein having reduced allergenicity, step "(b)" in instant base claim 7 and step "(d)" in instant base claim 12 is a modification step that effects neutralization of said T cell epitope and the wherein clause specifies that one of SEQ ID NO: 1-5 is what is neutralized or modified, whereas in contrast, the other method steps in both said instant base claims are essentially identification steps to identify what is already known to be the epitope to be neutralized in order to reduce immunogenicity.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used to reduce the immunogenicity of any BMP protein or to produce any BMP variant protein having reduced allergenicity.

The specification does not disclose which proteins or BMP proteins comprise at least one of SEQ ID NO: 1-5, except for BMP-7.

The specification discloses that SEQ ID NO: 1-5 were identified as originating from BMP-7 protein and are 15-mer peptides from an overlapping PEPSET of BMP-7 that can induce T cell proliferation (see Table 1 and Examples).

The specification discloses that there are at least fifteen BMP proteins (see page 1 at lines 21-36 and page 2 at lines 1-29), each having a different length and amino acid

sequence, and some that have been identified in different species of mammals. The specification further discloses that "Bone morphogenetic protein" ("BMP") is the generic term used to refer to a family of proteins originally identified in demineralized bone extracts...While the term "BMP" is indicative of their properties, these proteins also have other functions and are involved in processes other than bone formation" (see page 1 at lines 15-19).

Evidentiary reference Walker *et al* (Neurosurg. Focus, 2002, 13(6): 1-13, admitted prior art on page 27 of the specification at lines 22-23 and provided in the prior Office Action of record) teach that there are at least fourteen BMP subtype proteins and that the amino acid sequences of the mature segment of the different BMP subtypes vary (especially Table 1 and paragraph spanning columns 1-2 on page 2).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 7-10 and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 12 recites "said T-cell epitope" at the 3rd line from the end in part "(d)". There is insufficient antecedent basis for these limitations in the claim, as the recitation in the prior portions of the claim recite "T-cell epitope region".

b. Claim 7 recites the limitations listed in part "(a)", which part recites a series of steps for "identifying at least one T-cell epitope" in a BMP protein. There is insufficient antecedent basis for this limitation in the claim, as the claim preamble is a method of reducing the immunogenicity of a BMP protein and the claim further recites wherein the protein is modified to neutralize at least one T cell epitope that is one of SEQ ID NO: 1-5. Applicant should amend the claim to recite that the method of reducing the immunogenicity of a BMP protein comprises modifying said protein to neutralize a T cell epitope that is one of SEQ ID NO: 1-5 to produce a variant protein such as in step "(b)" of the instant claim, if that is what is meant, without recitation of the identifying steps in part "(a)".

c. Claim 12 recites the limitations listed in parts "(a)"-"(c)", which parts recite a series of steps for obtaining a BMP protein, preparing and contacting fragments thereof and identifying an epitope region. There is insufficient antecedent basis for these limitations in the claim, as the claim preamble is a method for producing a variant protein having reduced allergenicity that further comprises a step"(d)" to modify at least

one amino acid [residue] in the identified epitope region, and the claim further recites wherein the amino acid sequence of the T-cell epitope" is one of SEQ ID NO: 1-5. Applicant should amend the claim to recite that the method for producing a variant protein having reduced allergenicity comprises modifying at least one amino acid residue of one of SEQ ID NO: 5, if that is what is meant, without recitation of the identifying steps in part "(a)"-"(c)".

10. Applicant's amendment filed 7/22/11 has overcome the prior rejection of record of claims 7-16 under 35 U.S.C. 103(a) as being unpatentable over WO 02/077187 A2 in view of admitted prior art on page 27 of the description at lines 20-25 (Walker and Wright., Neurosurg. Focus 13(6): 1-13, 2002) and Paul (Fundamental Immunology 4th Edition, 1999, page 12, Lippincott-Raven Publishers, Philadelphia/New York), as evidenced by an admission in the specification on page 32 at lines 14-19 and on page 35 at Table 1.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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